

## Review

**Biventricular pacing in heart failure: update on results from clinical trials**

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Published online: 28 November 2001

*Curr Control Trials Cardiovasc Med* 2001, **2**:292-297

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**Abstract**

Biventricular pacing or resynchronisation therapy is a non-pharmacological therapy for patients with chronic heart failure. Since being originally described in 1994, biventricular pacing has become a subject of intense interest and investigation. This review analyses the results reported in observational series and randomised trials, and seeks to answer two questions. If it works, why does it work? Which heart failure patients will it benefit?

**Keywords** biventricular, heart failure, pacing, randomised trials, review

Pacing therapies for heart failure, which involve stimulating the left ventricle, have come to occupy centre stage at international cardiology conferences in the past 2 years. These types of therapy are generally referred to as 'biventricular pacing' or 'resynchronisation therapy'. They involve pacing the left ventricle, generally in addition to the right ventricle and the right atrium. The high level of interest is understandable, as the prospect of a new therapy that may provide significant symptomatic benefit to patients with drug refractory heart failure is clearly desirable. The therapy presents cardiologists who implant pacemakers with an enticing new technical challenge, making biventricular pacing even more attractive.

This article aims to review the background to this research, to analyse the published and recently announced trial results, and to address the two most pressing questions about biventricular pacing. If it works, why does it work? Which heart failure patients will it benefit?

**Background****Pacing and atrioventricular delay**

In the 1980s, interest in pacing therapy for heart failure largely revolved around manipulation of the atrioventricular (AV) delay in patients with heart failure who were implanted

with dual-chamber pacemakers using right atrial and right ventricular leads. Shortening the AV delay appeared to be beneficial in patients with first-degree AV block and in those with Doppler evidence of presystolic mitral regurgitation [1,2]. Individual patients appeared to show marked clinical improvement, but no benefit was found in patients with New York Heart Association (NYHA) class III or IV heart failure in long-term follow-up in controlled, randomised trials [3,4].

**Multisite pacing**

Early reports of biventricular pacing involved epicardial left ventricular (LV) leads. In 1994, Cazeau *et al.* reported a patient with refractory heart failure who had responded to four-chamber pacing [5]. In 1995, Foster *et al.* investigated pacing following coronary artery bypass graft, using different combinations of cardiac chambers with epicardial leads [6]. The authors found that maximal haemodynamic benefit was derived from a combination of atrial and biventricular pacing. It was known that patients with heart failure frequently had dysynchronous contraction of the cardiac chambers [7]. The underlying concept of resynchronisation therapy was that the efficiency of the heart as a pump would be increased if the start of systole could be synchronised by simultaneously pacing the two atria, followed by the ventricles.

**Table 1****On-table haemodynamic results of biventricular pacing [10]**

	AAI	DDD	Biventricular paced
Cardiac index (l/min/m <sup>2</sup> )	2 ± 0.5	2.4 ± 0.6	2.7 ± 0.7
Pulmonary capillary wedge pressure (mmHg)	27 ± 9	24 ± 5	22 ± 8

This hypothesis was tested in 'on-table' haemodynamic studies. The tests consistently showed increases in cardiac output and decreases in pulmonary capillary wedge pressure when patients were switched from right ventricular pacing to simultaneous biventricular pacing (Table 1) [8–10].

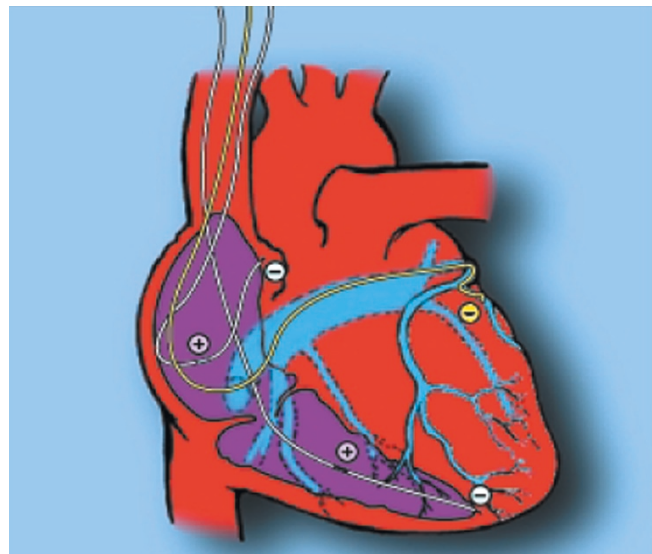
In 1998, Daubert *et al.* reported in the journal *PACE* that the LV free wall could be effectively paced on a long-term basis by a transvenous technique [11]. The authors reported introducing a unipolar lead via the coronary sinus and positioning the tip in an epicardial vein on the lateral wall of the left ventricle as part of a permanent pacing system (Fig. 1). This raised the possibility of delivering the haemodynamic benefits demonstrated in the acute on-table studies as a permanent therapy without the morbidity associated with thoracotomy techniques. Daubert *et al.* christened this new approach to the treatment of patients with heart failure 'resynchronisation therapy'.

A number of trials were initiated from this point onwards. Some were observational studies of series of patients undergoing biventricular pacing [12,13]. Other trials involved randomisation to biventricular pacing or no pacing – single blinded, as in the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial [14], or double blinded, as in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial [15].

### Recent trial results

Some of the results of these recent trials have been published in peer-reviewed journals, others have been reported as abstracts, and some have only recently been announced at 'late breaking trial results' sessions at international meetings. The data currently available are presented in Table 2. It should be emphasised that some of this is preliminary data, which may change after the follow-up is completed in these studies.

Although much of this data has not yet been peer reviewed, and may only reflect preliminary findings before follow-up, it is clear that there is a high degree of consistency in the data so far available from trials. Of recent interest were the results from the MIRACLE trial presented by William Abraham at the North American Society of Pacing and Electrophysiology (NASPE) 2001 meeting. Both the patients and the physicians monitoring the progress of patients in the study were blinded to the pacing mode. This would seem to rule out the possibility that the benefits seen with pacing in the biventricular mode might all have been due to the increased expectation of

**Figure 1**

Pacing lead positions in transvenous biventricular pacing. Endocardial leads are positioned in the right atrium and right ventricle, and the left ventricle is paced via a lead passed through the coronary sinus to an epicardial vein on the free wall of the left ventricle.

good performance by the supervising physicians. Overall, it seems very likely that a real effect is being observed.

The average magnitude of the effect is modest, although very helpful, in terms of clinical improvement. The situation is almost certainly one in which some patients are showing marked clinical benefit, balanced by other patients with very little benefit.

In the absence of a clear understanding of the mechanisms by which clinical benefit is being achieved, biventricular pacing will remain a relatively crude therapy, dictated primarily by what is feasible rather than by aiming for a planned and individually tailored electromechanical goal.

### Theories underlying mechanisms: why does biventricular pacing work?

#### Optimisation of AV delay

Patients with heart failure and PR prolongation may be a subgroup who benefit from optimisation of atrioventricular (AV)

**Table 2****Summary of the trial results currently reported**

Trial	Number of patients	Randomised comparison	Increase in 6 min walk	Increase in VO <sub>2</sub> max/ejection fraction	Improved quality of life	Decreased hospital admissions
Bordeaux series [13]	47	No	Not done	No significant change	Functional class improvement	Not stated
InSync [12]	103	No	50 m ( $P = 0.01$ )	Not stated	45%	Not done
PATH-CHF [30]	42	Yes	60 m	VO <sub>2</sub> max increased 23%	Increased	Not stated
MUSTIC (SR) [14]	58	Yes	23% ( $P < 0.001$ )	8% ( $P < 0.03$ )	32% ( $P < 0.001$ )	3 admitted during biventricular pacing versus 9 during no pacing
MIRACLE [15]	370	Yes (patients and physicians)	35 m ( $P = 0.04$ )	Awaited	Small but significant ( $P < 0.002$ )	233 days (biventricular) versus 621 days (control) over 6 months
CONTAC CD	460 (33% NYHA class II)	Yes	No significant change	VO <sub>2</sub> max 9% increase; LV diameter 4 mm decrease ( $P = 0.001$ )	No significant change	Not stated

CONTAC CD, information from oral presentations at the North American Society of Pacing and Electrophysiology 2001 meeting; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; PATH-CHF, Pacing Therapies for Congestive Heart Failure; NYHA, New York Heart Association; LV, left ventricular.

delay. This optimization of the AV delay is thought to correct adverse compression of the diastolic filling time and to reduce presystolic mitral regurgitation [1,2]. Such patients may obtain this haemodynamic gain from adjustment to AV delay as part of a biventricular pacing system, so this could contribute to clinical improvement in such patients. This aspect of biventricular pacing is likely to play a part in a small subgroup only.

### Reduction in systolic mitral regurgitation

Reports of reduced mitral regurgitation with biventricular pacing appeared shortly after original descriptions of the transvenous technique [16]. This mechanism was investigated as part of the MIRACLE study. The preliminary presentation of results at the NASPE 2001 meeting [15] reported a reduction in the mitral regurgitation jet area from 7 to 4 cm<sup>2</sup> in the biventricular paced patients from baseline to 6 months, whereas the control group showed no change. Other investigators have observed similar reductions in the mitral jet area [17].

One possible explanation for this improvement in patients with so-called functional mitral regurgitation may be the change in the activation sequence of the LV chamber and papillary muscles. Contraction is normally from apex to base, but with biventricular pacing this pattern is reversed and the base contracts before the apical LV myocardium. This change may be consequent on the typically basal position of the LV lead in the part of the posterolateral LV vein close to the AV ring. This reversal of the contraction pattern has been demonstrated using radionuclide angioscintigraphy in patients with dilated cardiomyopathy, and appeared to correlate with long-term benefits from biventricular pacing [18].

### Increased efficiency of systolic function

It has been proposed that, because of the long delay in activation time from septal depolarisation to depolarisation of the LV free wall, contractile patterns can arise where the septal muscle is starting to relax as the left free wall enters systole. This is likely to result in reduced contractile efficiency, and tagged magnetic resonance angiography has confirmed the wobbling motion of the LV cavity in the setting of severe dilated cardiomyopathy and LV dilatation [19].

Correction of this problem by biventricular stimulation resulting in simultaneous activation of the septal and free wall muscle appears to result in increased arterial pulse pressure (increased by 18%) and LV dP/dT (increased 43%), with a decrease in the arteriovenous oxygen saturation (4% lower with biventricular pacing). This is a unique observation in patients with heart failure. All therapies capable of increasing systolic function have previously been associated with increased myocardial oxygen consumption and, in long-term follow-up, increased mortality. This is therefore an exciting initial observation requiring replication and further investigation.

### Diastolic ventricular interaction

Another potentially important mechanism is the reversal of adverse diastolic ventricular interaction by biventricular pacing. Patients with heart failure and left bundle branch block have a tendency for LV diastole to start markedly later than that in the right ventricle. Where the atrial filling pressures are raised and the heart is dilated, the pericardium will rapidly come close to its distensible limit during ventricular filling. The tendency is for the right ventricle to fill first,

expanding within the pericardial sac, resulting in an increased baseline pressure within the space enclosed by the pericardial sac at the start of LV filling. This results in decreased LV filling, as the amount of filling will be dependent on the pressure difference between the left atrial pressure and the pressure within the LV cavity. This pressure difference is determined by the sum of the hydrostatic pressure of blood within the left ventricle and the pressure exerted externally on the walls of the LV by the pre-existing pressure within the pericardial space. Pacing the left ventricle before the right reverses this problem as the LV enters diastole first and starts to fill when the pressure in the pericardial space is at the lowest point. This mechanism is therefore an argument for LV pacing rather than biventricular pacing, and some groups have tested the hypothesis that this is the principle mechanism of benefit in LV pacing without stimulation of the right ventricle [20,21].

### Anti-arrhythmic effects

Some preliminary data suggest that, alongside improvement in ventricular function, there may be a beneficial effect on ventricular arrhythmias. The Ventak CHF study [22] randomised 32 patients to 3 months of either no pacing or biventricular pacing. Thirty-four percent of patients without biventricular pacing over this period experienced at least one ventricular tachyarrhythmia; in contrast, only 16% of patients with biventricular pacing had an episode of ventricular tachyarrhythmia. Walker *et al.* studied ventricular ectopic frequency in the different pacing modes in heart failure patients who had undergone biventricular pacing, and have reported similar evidence of benefit [23].

### Effects on mortality

The mortality rate in trials such as the MUSTIC trial was lower than might have been predicted for NYHA class III–IV heart failure patients. A mortality rate of 7.5% over 7.5 months was reported for patients with sinus rhythm. There are now large-scale trials underway, such as the Cardiac Resynchronisation in Heart Failure trial, which are powered and designed to answer the question whether there is a significant mortality benefit from biventricular pacing additional to the combined mortality benefit from optimised heart failure drug therapy.

### Myocardial remodelling

Over the past decade there has been intensive investigation, at a molecular level, of the underlying myocardial environment in patients who have molecular processes leading to progressive, adverse remodelling. It may be that a change in wall stress and energy consumption, of even a small degree, might be enough to halt or reverse a downhill slide, and reverse adverse patterns of gene expression. As such, remodelling is likely to involve different processes at a cellular level; patients with completely different pathologies, such as ischaemic heart disease or dilated cardiomyopathy, may respond very differently to the changes in the pump efficiency likely to be achieved by biventricular pacing. While little infor-

mation exists in relation to any such modulation of molecular processes by biventricular pacing, a direct effect on critical influences on myocardial receptors such as sympathetic nervous system activation has been documented [24].

In addition to different effects at a molecular level, it may also be necessary in patients with ischaemic heart disease to apply the therapy in a more individual regional fashion. Patients who have suffered myocardial infarction in different territories may have different wall motion and papillary muscle problems.

### Limitations to the technique

The most frustrating aspect of biventricular pacing is probably when it proves difficult to cannulate the coronary sinus os with the guide sheath. This may be due to the limited shapes of guide sheaths available and insufficient stiffness for placement of the LV lead. This difficulty results in situations where the coronary sinus can be cannulated with a diagnostic catheter, such as an AL2, but when the sheath is advanced, even when the locating catheter and guidewire are in the coronary sinus, there is a tendency for the system to become displaced. Approaches are being developed to mount a more flexible-tipped sheath on a steerable guide similar to a radiofrequency ablation catheter, which should help with this problem in difficult cases where right atrial dilatation and distortion of the usual position is present.

Another area of difficulty is selecting the optimal vein for lead placement. This has been made easier with leads deployed using an angioplasty guidewire technique, although entry to veins with an adverse angle onto the junction with the coronary sinus is still a problem. This can require cannulation of the side branch with a diagnostic catheter with a sharply angled tip, such as a JR4, preferably in as flexible and soft a version as possible, to avoid trauma to the vein. Once the wire is placed, it may then be possible to steer the electrode around the sharp bend. This technique is helped by reducing the length of the diagnostic catheter for ease of manipulation.

Finally, problems with thresholds and phrenic nerve stimulation can occur. Leads with narrow tips, which need to be fixed by friction against the vein wall, can end up having to be pushed too far towards the LV apex in large posterolateral veins, causing phrenic nerve stimulation common in this site. It is also possible that the loss of base to apex activation in this situation may decrease the effectiveness of the technique. To counter this problem, in suitable veins of large calibre, there are now leads that produce a preformed spiral shape on stylet removal, allowing the lead to press against the walls of a relatively large calibre vein.

Each procedure should ideally be planned once the coronary sinus angiogram has been obtained. This requires a range of electrodes to be available for each procedure. This approach is necessary even if coronary sinus imaging has been

obtained prior to the procedure, as it is sometimes difficult to predict which lead will achieve stability with good thresholds in a suitable vein position.

Venous access may be difficult in some cases and a left subclavian venogram may be valuable for imaging the vein on the side of intended placement. It is helpful to check that a reasonable sized vein without major anomalies is present before embarking on either triple subclavian puncture or a combination of cephalic cannulation and venous puncture.

### How widely applicable is the technique? Who will respond?

Estimates of the numbers of patients that may be eligible for biventricular pacing have been based on the percentage of symptomatic heart failure patients with broad QRS complexes or other features associated with clinical benefit in trials. The numbers have been estimated from district hospital [25] and tertiary referral-based [26] populations at 10% and 14% of heart failure patients, respectively. These estimates are necessarily very speculative as there is little information yet available to allow accurate identification and selection of patients likely to achieve the best response from biventricular pacing.

The Bordeaux group found that non-responders were more likely to be older, to have an underlying aetiology of ischaemic heart disease, and to have no evidence of mitral regurgitation [13]. Like some other groups who have reported recently (e.g. the MIRACLE investigators) [15], the Bordeaux group found no correlation between baseline QRS duration and clinical response. There are, however, reports that responders have narrower biventricular-paced complexes than do non-responders (i.e.  $154 \pm 17$  ms versus  $177 \pm 26$  ms), which may indicate that benefit equates to more effective overall resynchronisation of activation times in the ventricles [27].

The Baltimore group recently reported an analysis of parameters predicting a positive response to biventricular pacing in 22 patients with dilated cardiomyopathy [28]. They made an on-table assessment using a LV micromanometer and measured  $dP/dT_{\max}$  during sinus rhythm and left free wall pacing. The study reported that a baseline QRS duration  $>155$  ms in association with  $dP/dT_{\max} < 700$  Hg/s predicted a percentage change of  $dP/dT_{\max}$  with LV pacing of greater than 25% and a percentage change in arterial pulse pressure of greater than 10% with no false positives. This was an acute study and the analysis needs to be examined in permanently implanted patients.

Another technique that shows promise in identifying responders is Tissue Doppler Imaging (TDI) (or tissue velocity imaging). In a recently reported study of 21 patients undergoing biventricular pacing, improvement in TDI measurements of the synchrony of LV segment contraction was associated with clinical improvement, exercise time improvement and LV ejection fraction improvement. Patients without

improved TDI measurements showed no benefit from biventricular pacing [29].

Aside from the question of identifying patients likely to respond to biventricular pacing, there are also questions of proper training in the technique, and availability of cardiac catheter laboratory time. For the present, these factors may play an important part in determining how widely the technique is applied. If an operating theatre with a C-arm is used it can be difficult to achieve adequate left anterior oblique and right anterior oblique projections for facilitating coronary sinus entry and lead manipulation, because most pacing and operating theatre tables have metallic sides that make imaging in oblique planes difficult. Manoeuvrability of the C-arm is also limited. In practice, the technique is likely to be confined to those cardiac catheter laboratories that have the very high level of sterility required to avoid infection in situations where the pre-pectoral wound may be open for 2 hours. While the experienced operator will expect shorter operative times, there will necessarily be a learning curve where, at first, procedure times will be prolonged, taking up a whole morning or afternoon session.

There is also the question of the cost of the systems. At present in the UK a biventricular system is usually supplied for a total cost of approximately £4500, which is about 50% more than the cost of a standard dual-chamber system. While different centres may be able to negotiate advantageous prices with suppliers and while there are significant variations in the costs of pacing systems in different countries, the increased cost is likely to be a significant obstacle to increasing the availability of this therapy in some health care environments.

### Conclusions

Trials of biventricular pacing indicate a fairly consistent pattern of symptomatic benefit in patients with NYHA class III–IV heart failure. Effects on mortality will not be clearly determined until the results of trials addressing this question are reported in 3–4 years time. The technique is gradually becoming easier to deliver and, in the absence of contradictory or adverse trial results and in the absence of the emergence of an alternative therapy for such patients, it is likely to become an essential part of training in complex pacing and heart failure management.

### Competing interests

None declared.

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